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Outcomes from second-line therapy in long-term responders to first-line tyrosine kinase inhibitor in clear-cell metastatic renal cell carcinoma

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Background: Although sequential targeted therapy is standard in patients with metastatic clear-cell renal cell carcinoma (m-ccRCC), the choice of drugs and optimal administration sequence have yet to be established. The objective of this study was to explore whether it is preferable to rechallenge a long-term responder to a first-line tyrosine kinase inhibitor (TKI) with a TKI or whether to switch to a mammalian target of rapamycin inhibitor (mTORi); to determine whether second-line treatment response depends on duration of first-line response (TD1).

Patients and methods: Retrospective multicenter study (2004–2011) of 241 consecutive mRCC patients (clear-cell histology) who received a first-line TKI for ≥6 months followed by a second-line TKI ($n = 118$) or mTORi ($n = 123$). End points: Progression-free survival (PFS) and time-to-treatment failure (TTF) on second-line therapy. Multivariable full-model: second-line drug, TD1, ECOG-PS before first- and second-line, best objective response (first-line), Fuhrman grade, number of metastatic sites, and presence of bone metastases. Adjustment covariable: International mRCC Database Consortium (IMDC) risk score. Multiple propensity score and missing data methods were used. Any correlation between first-line and second-line PFS was investigated using censored quantile regression models (CQRM).

Results: Sequence effect in the overall cohort was in favor of the TKI–TKI sequence over the TKI–mTORi sequence on using TD1 as continuous covariable (HR ≈ 0.75 for PFS and TTF). TKI–TKI superiority was attributed in large part to the 11–22 month (TD1) subgroup of patients which displayed significantly better outcomes [HR ≈ 0.5; median PFS (months): 9.4 (5.9–12.2) versus 3.9 (3.0–5.5), $P = 0.003$; TTF(months): 8.0 (5.5–11.0) versus 3.6 (3.0–4.6), $P = 0.009$]. Upon full CQRM, long-term second-line responders were more likely to have received a second TKI than an mTORi and to have been long-term responders to first-line TKI.

Conclusions: m-ccRCC patients who remained on first-line TKI between 11 and 22 months benefited from a TKI rechallenge rather than from second-line mTORi.

Key words: kidney cancer, mammalian target of rapamycin (mTOR), sequence, tyrosine kinase inhibitor

introduction

Guidelines for the second-line treatment of patients with metastatic clear-cell renal carcinoma (m-ccRCC) who have failed first-line treatment with tyrosine kinase inhibitors (TKIs) targeting vascular endothelial growth factor receptor (VEGFR) (sunitinib, sorafenib, or pazopanib) recommend administration either of an inhibitor of the mammalian target of rapamycin (mTORi), in particular everolimus, or of the TKI axitinib [1, 2]. The evidence underlying these guidelines, however, remains sparse [3–8].

Randomized trials have tested several drug sequences. The RECORD-3 phase II trial comparing first-line everolimus followed by second-line sunitinib versus the reverse sequence did not demonstrate everolimus noninferiority versus sunitinib as first-line but concluded in favor of the standard paradigm of

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sunitinib followed by everolimus [9]. In the AXIS phase III trial comparing second-line axitinib to sorafenib, regardless of first-line treatment, progression-free survival (PFS) but not overall survival (OS) was better with axitinib [10]. On the other hand, the INTORSECT phase III trial comparing second-line temsirolimus to sorafenib after TKI failure found no difference in primary end point (PFS) but a benefit in secondary end point (OS) for sorafenib [11].

A retrospective review conducted by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) of 464 patients receiving different TKIs as first- and second-line therapy detected no correlation between first- and second-line PFS [12]. However, a recent subgroup analysis of the AXIS trial showed that outcome to second-line therapy is better when duration of first-line treatment is longer but underlined that, for a given agent, prior response and length of therapy were not convincing enough to help select second-line treatment [13]. A small retrospective study has suggested that long-term responders to a first TKI who received a second-line TKI instead of everolimus had better outcomes in terms of median PFS with the second agent [14]. It has been suggested that the short- or long-term response to a first-line TKI should guide optimal choice of second-line agent [15].

None of the above studies focused specifically on long-term responders. This in-depth retrospective analysis explores: (i) whether it is preferable to rechallenge a long-term responder with a TKI or whether to switch to an mTORi, (ii) whether duration of first-line response may help select second-line therapy.

patients and methods

patient population

Data were retrospectively collected from the medical records of consecutive m-ccRCC patients receiving sequential targeted therapy in 10 institutions in 4 European countries (2004–2011) after obtaining approval for the study from the institutions' ethics committees. At least 10 eligible patients per institution were needed for participation. Eligibility criteria were: clear-cell histology and at least 6.0 months on first-line TKI followed by second-line treatment with a TKI or an mTORi. Discontinuation of first-line treatment due to toxicity was not a reason for exclusion as long as the ≥6 months eligibility criterion was met. Exclusion criteria were unclear reasons for discontinuing second-line therapy as well as treatment other than short-term palliative procedures intervening between first- and second-line targeted therapies. No semicurative cytoreductive surgery or stereotactic radiotherapy was carried out during therapy. Immunotherapy before first-line TKI was allowed.

data collected

We recorded demographics, histology, cancer history, sequential drugs use with duration, best objective response upon Response Evaluation Criteria In Solid Tumors (OR), reasons for first- and second-line discontinuation, and data for calculating pretreatment prognostic scores [Memorial Sloan-Kettering Cancer Center (MSKCC) and IMDC [16, 17]].

study end points

The main end point was PFS on second-line therapy with censoring of patients who discontinued because of toxicity or for a therapeutic break, regardless of any subsequent radiological disease progression. The secondary end point was time-to-treatment failure (TTF) with censoring of patients still undergoing treatment at last contact.

statistical analysis

Survival estimates were obtained by the Kaplan–Meier method. First-line TKI treatment duration (TD1) was introduced as a continuous covariable. Fixed TD1 intervals of either 6 or 11 months (i.e. 6–12, 12–18, 18–24, ≥24 months or 6–11, 11–22, ≥22 months, respectively) were also considered. The relationship between sequence effect and time-to-event end points was investigated using a Cox proportional-hazards regression model adjusting for the following covariables: TD1, age at initial diagnosis, Fuhrman grade score, number of metastatic sites, presence of bone metastases, OR on first-line therapy, and ECOG-PS (Eastern Cooperative Oncology Group performance status) before first- and second-line therapy. We used a full-model approach (no prior variable selection) to avoid biased standard errors and overoptimistic effects. Bias-corrected hazard ratios with confidence intervals were obtained from 1000 bootstrap samples. We analyzed several datasets for impact of missing data on outcomes: (i) complete-case analysis (deletion of patients with ≥1 missing datum), (ii) full-information maximum likelihood estimation, (iii) multiple imputation using fully conditional specification, (iv) worst-case analysis with either TKI-worst or mTORi-worst.

We applied several methods: (i) to offset a possible between-sequence imbalance in patient characteristics and account for reasons for first-line TKI discontinuation, we used propensity scores (PSc) with either Inverse Probability of Treatment Weighting or Quintile Stratification, with IMDC risk score as an adjustment covariable in addition to other covariables; (ii) to capture heterogeneous effects of second-line therapy and of TD1 on PFS and TTF distribution, we used a full-model censored quantile regression based on Kaplan–Meier estimator of the cumulative hazard function to fit Log(PFS/TTF); (iii) to test for delayed everolimus entry bias, we used a stratified log-rank test; (iv) to manage short follow-ups, we conducted a sensitivity analysis for censoring. Details are provided in the supplementary Material, available at *Annals of Oncology* online. The *P*-value for statistical significance was 0.05. We used SASv9.3 (NY, Cary) and Mplus6 (Muthén & Muthén) for full-information maximum likelihood estimates.

results

patient characteristics

Overall, 313 patients who had received sequential targeted therapy starting with a first-line TKI were screened for eligibility [France ($n = 222$), Belgium ($n = 49$), Greece ($n = 30$), and Italy ($n = 12$)]. Seventy-two patients were excluded (see Flowchart, supplementary Figure S1, available at *Annals of Oncology* online). The main reason (82%) was a TD1 <6 months (5.5–5.9 months).

Patients' baseline characteristics and response to first-line TKI are given in Table 1. Among 241 eligible patients, 206 (85%) experienced progressive disease (PD) while on first-line TKI and 14 (6%) after discontinuation for toxicity or a break from therapy. Overall, 35 patients (TKI–TKI = 19; TKI–mTORi = 16) discontinued for reasons other than PD. A total of 118 patients received second-line TKI whereas 123 patients received mTORi (some received everolimus within the RECORD-1 trial or the REACT expanded access program). Patient characteristics at initiation of second-line therapy were well balanced (Table 1) with, however, a higher proportion of poor-risk group patients receiving TKI–mTORi. PD on second-line therapy occurred in 97 TKI–TKI and 96 TKI–mTORi patients (censoring rate 17.8% and 21.9%, respectively); median follow-up was 35.1 [interquartile range

Table 1. Patients' characteristics at baseline and on initiation of second-line therapy, and outcomes on first-line therapy

	All patients (n = 241)	TKI–TKI (n = 118)	TKI–mTORi (n = 123)
Baseline characteristics on first-line TKI therapy			
Median age at diagnosis (IQR), years	58 (53–65)	56 (51–63)	59 (54–66)
Sex ratio (male/female)	2.8	2.9	2.7
Fuhrman grade, n (%)			
1–2	52 (25)	27 (27)	25 (23)
3–4	156 (75)	74 (73)	82 (77)
Missing	33	17	16
Nephrectomized, n (%)	231 (96)	115 (97)	116 (94)
Missing	1	0	1
Number of metastatic sites, n (%)			
1–2	160 (66)	81 (69)	79 (64)
>2	81 (34)	37 (31)	44 (36)
Presence of bone metastases, n (%)	56 (23)	25 (21)	31 (25)
ECOG-PS, n (%)			
0	131 (59)	69 (63)	62 (54)
1–3	93 (41)	41 (37)	52 (46)
Missing	17	8	9
Risk group: MSKCC/IMDC, n (%)			
Favorable	41 (21)/37 (18)	19 (20)/20 (20)	22 (22)/17 (16)
Intermediate	117 (60)/04 (52)	59 (63)/54 (56)	58 (57)/50 (49)
Poor	37 (19)/59 (30)	16 (17)/23 (24)	21 (21)/36 (35)
Missing	46/41	24/21	22/20
Median time since diagnosis (range), years	2.25 (0–27.5)	2.9 (0–24.8)	1.9 (0–27.5)
First-line TKI, n (%)			
Sunitinib	202 (83)	93 (78)	109 (89)
Sorafenib	37 (15)	25 (21)	12 (10)
Pazopanib	2 (0.8)	0	2 (1.6)
Outcomes on first-line TKI therapy			
Best response, n (%)			
Complete response	1 (0.4)	0	1 (0.8)
Partial response	99 (42)	42 (37)	57 (48)
Stable disease	133 (57)	73 (63)	60 (51)
Missing	8	3	5
Reason for discontinuing TKI, n (%)			
Progressive disease	206 (85)	99 (84)	107 (87)
Toxicity	20 (8.3)	9 (7.6)	11 (8.9)
Other (break/surgery/radiotherapy)	15 (6)	10 (8)	5 (4)
Median TD1 (95% CI), months	14.6 (12.8–17.2)	14.7 (12.1–17.5)	14.2 (12.4–18.8)
TD1 stratification, n (%)			
6–11 months	80 (33)	39 (33)	41 (33)
$\geq$11–22 months	93 (39)	51 (43)	42 (34)
$\geq$22 months	68 (28)	28 (24)	40 (32)
Characteristics on initiation of second-line therapy			
ECOG-PS, n (%)			
0	75 (34)	38 (37)	37 (32)
1–3	143 (66)	65 (63)	78 (68)
Missing	23	15	8
Risk group: MSKCC/IMDC, n (%)			
Favorable	11 (6)/10 (5)	6 (7)/6 (6)	5 (5)/4 (4)
Intermediate	123 (64)/121 (60)	65 (74)/63 (67)	58 (56)/58 (54)
Poor	57 (30)/71 (35)	17 (19)/25 (27)	40 (39)/46 (43)
Missing	62/39	34/24	28/15
Second-line treatment, n (%)			
Sunitinib	32 (13)	32 (27)	–
Sorafenib	82 (34)	82 (69)	–
Pazopanib	1 (0.4)	1 (0.8)	–

Continued

Table 1. *Continued*

	All patients (n = 241)	TKI–TKI (n = 118)	TKI–mTORi (n = 123)
Axitinib	3 (1.2)	3 (2.5)	–
Everolimus	109 (45)	–	109 (89)
Temsirolimus	14 (6)	–	14 (11)

Percentages are rounded to nearest integer and given as percentages of nonmissing values. Correlation between ECOG-PS and Karnofsky PS (when available): χ^2, $P < 0.0001$.

IQR, interquartile range; TKI, tyrosine kinase inhibitor; mTORi, mTOR inhibitor; ECOG-PS, Eastern Cooperative Oncology Group performance status; TD1, first-line treatment duration; TTF1, time-to-treatment failure on first-line therapy; CI, confidence interval; MSKCC, Memorial Sloan-Kettering Cancer Center risk group; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium risk group.

(IQR): 20.8–70.9] and 22.9 (IQR: 13.4–30.6) months, respectively; 7 (5.9%) and 13 (10.5%) patients on second-line therapy were censored for TTF [median follow-up, 20.3 (IQR: 11.7–35.1) and 9.6 (IQR: 5.5–22.9) months, respectively].

second-line outcomes

When using TD1 as a continuous covariable for the whole cohort, the sequence effect was in favor of the TKI–TKI sequence over the TKI–mTORi sequence, regardless of dataset. The HR averaged over all datasets was 0.75 for both PFS (Figure 1A) and TTF (supplementary Figure S2A, available at *Annals of Oncology* online). The estimated benefit afforded by the TKI–TKI sequence was, however, mainly due to the 11–22 month TD1 subgroup in all datasets (Figure 1C, supplementary Figure S2C, available at *Annals of Oncology* online). The averaged HR in this subgroup was 0.5 for PFS and 0.65 for TTF, with significantly better outcomes for the TKI–TKI than TKI–mTORi sequence [complete-case dataset PFS: 9.4 (5.9–12.2) versus 3.9 (3.0–5.5) months, unadjusted $P = 0.003$; TTF: 8.0 (5.5–11.0) versus 3.6 (3.0–4.6) months, unadjusted $P = 0.009$] (supplementary Figure S3A and B, available at *Annals of Oncology* online). The averaged between-sequence difference in median PFS and TTF was 5.5 months (supplementary Table S1, available at *Annals of Oncology* online). Neither sequence predominated in the 6–11 month or >22 month subgroups (Figure 1B and D, supplementary Figure S2B and D, available at *Annals of Oncology* online). Similar results were obtained on exclusion of the 35 patients who discontinued for reasons other than PD.

substantiation of TKI–TKI sequence superiority

In a subgroup analysis of the full-model with no PSc, a significant interaction between second-line therapy and the 11–22 month TD1 subgroup was observed for PFS (but not TTF) for most datasets, supporting TKI–TKI superiority in this subgroup (Figure 2, supplementary Table S2, available at *Annals of Oncology* online). The 12–18 and 18–24 month TD1 subgroups also emphasized an advantage of the TKI–TKI sequence but lacked the power needed to reach statistical significance. Despite no PSc, there was no significant interaction between IMDC risk group and second-line therapy, thus excluding bias from between-sequence imbalance in risk before second-line therapy.

variable effects of second-line drug class and TD1 on second-line end points

The effect of the second-line drug and of TD1 might vary according to the PFS and/or TTF distribution on second-line therapy. We investigated linear models fitted to 25th (short-term), 50th (median-term), and 75th (long-term) PFS or TTF percentiles (PFS: 2.8, 5.5, and 13.3 months; TTF: 2.5, 4.9, and 11.2, respectively) over all datasets. The TKI–TKI sequence provided a 1.2–1.8 month gain in PFS and in TTF regardless of whether the patient was a short, median, or long-term second-line responder (Figure 3A, supplementary Figure S4A, available at *Annals of Oncology* online). The second-line drug effect was statistically significant in long-term responders for the complete-case and worst-case (TKI-worst) datasets, with or without PSc, for both PFS and TTF. The impact of TD1 on PFS was particularly clinically significant for PFS in the long-term second-line responders, with a 3-month gain per each additional 6 months on first-line therapy, compared with a 1.0–1.5 month gain in short- and median-term responders (Figure 3B, supplementary Figure S4B, available at *Annals of Oncology* online). In short, long-term second-line responders were more likely to have received a second TKI and to have been long-term responders to first-line TKI.

discussion

According to our analysis, patients who received a first-line TKI for at least 6 months benefited more from TKI rechallenge than from a switch to an mTORi. However, this observation applied primarily to the patient subgroup on first-line TKI between 11 and 22 months. The sequence effect was consistent across a series of datasets. Although the better tolerance of mTORi over TKI may have led to mTORi being reserved for less fit and TKI for fitter patients, we found that risk group did not impinge on sequence effect in patients with long-term responses.

Our findings are consistent with those of several earlier retrospective studies: (i) in a comparison of TKI–TKI–everolimus versus TKI–everolimus–TKI ($n = 19$ versus 14), only patients with a >9-month first-line TKI response experienced a 7.5-month gain in second-line PFS ($P = 0.02$) [14]; (ii) in a comparison of VEGF-targeted versus mTORi therapy after first-line VEGF-targeted therapy ($n = 192$ versus 24), VEGF-targeted therapy yielded a 2.3-month gain in TTF ($P = 0.014$) [18].

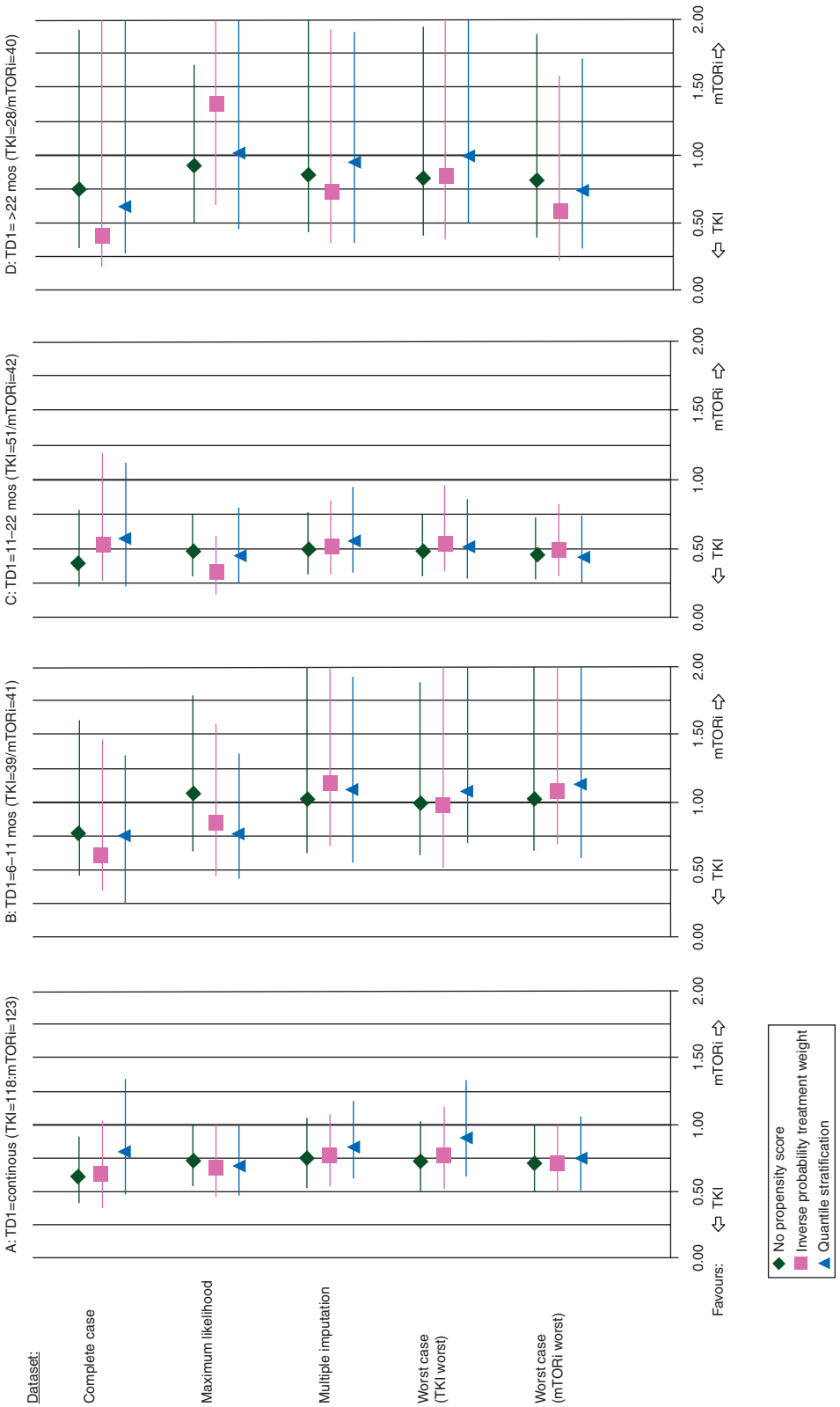

Figure 1. Sequence effect (hazard ratio with 95% CI) for second-line progression-free survival (per dataset, with or without propensity score): (A) TD1 as continuous covariable, (B) TD1: 6–11 months, (C) TD1: 11–22 months, (D) TD1: >22 months (TD1: first-line TKI treatment duration). CI: confidence interval; TD1, first-line treatment duration.

When adjusted on first-line therapy, the TTF difference favored rechallenge (HR = 0.481, $P = 0.016$); (iii) in a comparison of sunitinib–sorafenib–everolimus versus sunitinib–everolimus–sorafenib ($n = 71$ versus 56), the former sequence provided a significant PFS gain [PFS: 11.2 and 7.7 months for sunitinib (28% patients) and sorafenib (33%), respectively, and 4.8 and

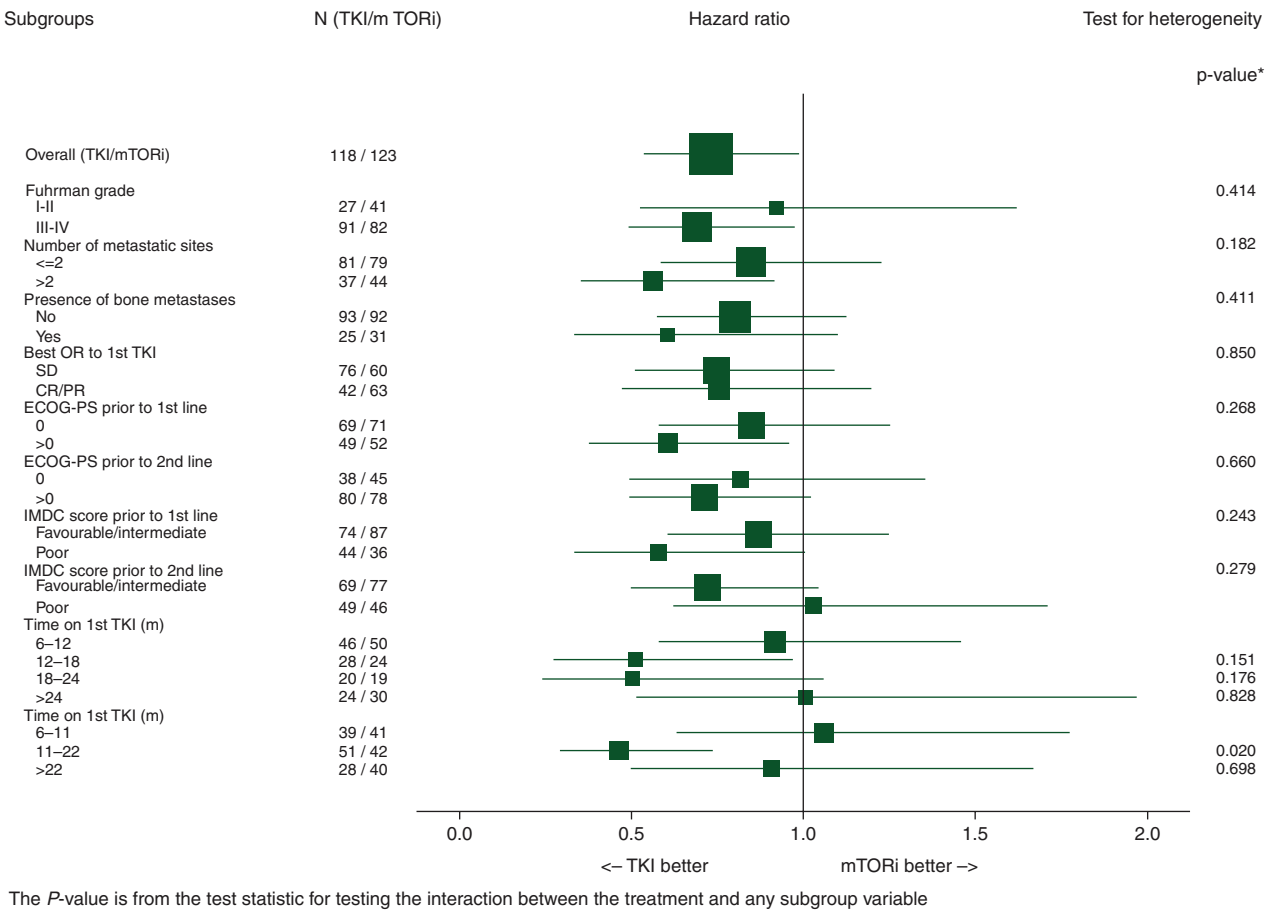

Figure 2. Subgroup analysis of sequence effect (progression-free survival as end point, full-information maximum likelihood dataset, no propensity score).

3.6 months for everolimus (28%) and temsirolimus (10%), respectively, $P = 0.006$] [19]. Our median PFS values of 7.3 and 5.2 months for second-line TKI and mTORi, respectively, support these results.

Some studies have detected no difference between second-line targeted therapies. A study of second-line TKI and mTORi ($n = 41$ versus 42) in first-line TKI failures found both treatments to be as effective in terms of PFS and OS [20]. Everolimus showed no clear benefit in a comparison of VEGFi–TKI–mTORi versus VEGFi–mTORi–TKI ($n = 62$ versus 41) [21] although it improved OS, but not PFS, in a comparison of VEGFi–TKI versus VEGFi–mTORi ($n = 46$ versus 62) by the same team [22]. In the INTORSECT trial, there was no significant difference in median PFS between sorafenib and temsirolimus (HR = 0.87, $P = 0.19$) although sorafenib improved OS [11].

Our findings differ from those of two large-scale retrospective reviews in favor of the TKI–mTORi sequence: (i) In a study of 257 sunitinib-treated patients, risk of second-line treatment failure was significantly higher with temsirolimus and with sorafenib than with everolimus [23]; (ii) in a medical record review of second-line everolimus, temsirolimus, and sorafenib after a TKI ($n = 233$, 178, and 123, respectively), everolimus was associated with numerically prolonged PFS compared with sorafenib [24]. It should be stressed, however, that temsirolimus, unlike everolimus, is usually reserved for poor prognosis patients. Moreover, these reviews overlooked first-line TKI response. Only the AXIS trial subgroup analysis has considered first-line TKI response (9.7-month cut-off) when evaluating the benefit of a second-line TKI [13].

To our knowledge, previous line treatment duration is rarely used as a covariable when modeling subsequent lines. In our study, sequence effect depended on the side of the second-line response distribution being modeled. The TD1 effect was more stringent in long- rather than short-term second-line responders. Characterization of *a posteriori* long-term responders in studies involving a third line might help substantiate this observation.

The mechanisms underlying our results require elucidation. If VEGF/VEGFR-driven angiogenesis remains a key feature of advanced disease and a TKI has a more direct antiangiogenic action than an mTORi, then TKI superiority over mTORi may not be that surprising. An antiangiogenic effect might be the primary mechanism of action of mTORi in mTORi-treated m-ccRCC patients, other than those with 'metabolic' RCCs harboring mTOR gene mutations [25]. After failure of a first TKI, continued kinase suppression of persisting TKI-sensitive clones might slow down disease progression [26]. On the other hand, the 6–11-month TD1 subgroup might have developed resistance to TKI or had faster growing tumors [27] whereas the >22-month TD1 subgroup might have had more indolent disease less sensitive to drug type. Why TTF, unlike PFS, did not reach statistical significance in the subgroup analysis in all datasets remains, however, unclear.

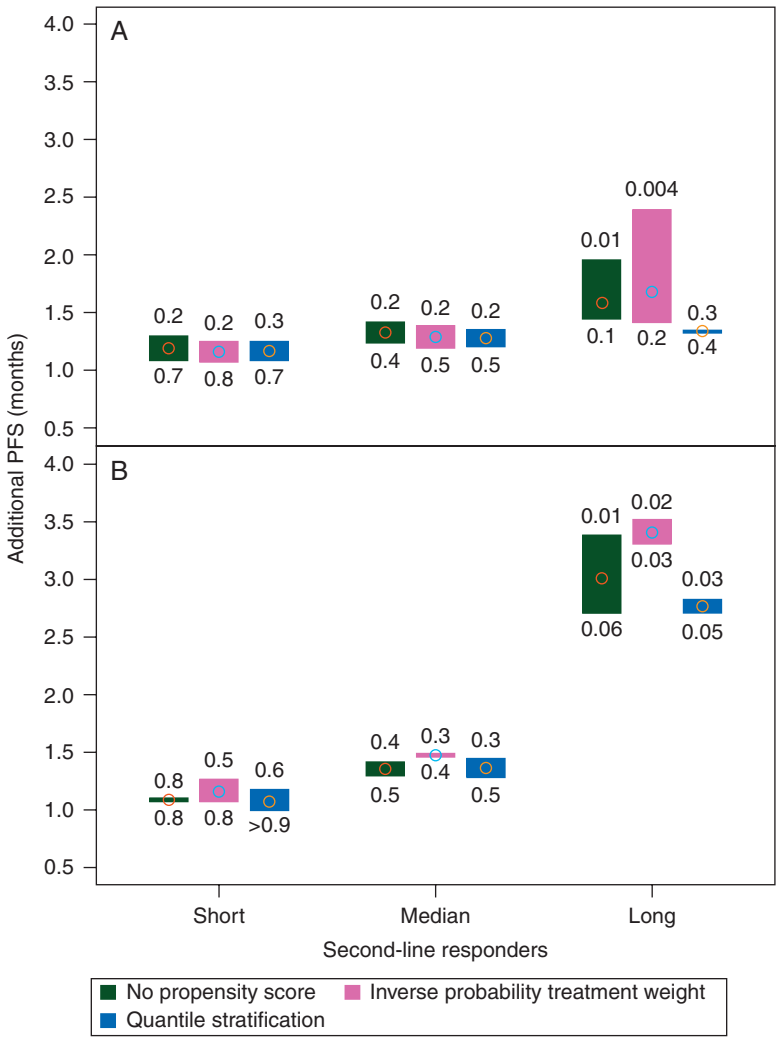

Figure 3. Gain in progression-free survival in short, median, and long-term second-line responders: (A) On administering a TKI versus an mTORi; (B) for each additional 6 months in TD1. Extreme *P*-values of the effect estimate in the different datasets are shown above and below the high–low plots.

The methodological strengths of our study are: (i) a homogeneous multicentric cohort of m-ccRCC patients receiving a first-line TKI for ≥6 months; (ii) well-balanced treatment groups; (iii) compensation for loss in statistical power from exclusion of patients with missing data in the complete-case dataset by analysis of four extra datasets (the similarity in results across datasets confirmed that missing data did not impact on overall sequence effect and that the missing completely at random assumption was reasonable); (iv) adjustment by PSc for any bias due to between-sequence imbalance in risk before second-line treatment. In any case, risk group had no impact on the relationship between sequence and outcome (PFS or TTF). The benefit of a second-line TKI remained significant even on worst-case analysis favoring the TKI–mTORi sequence (virtually restoring balance in poor prognosis patients who tended to receive mTORi more often). Moreover, the interaction term between risk group and sequence was not significant.

Our study has limitations: (i) a retrospective design but one that reflects real-life clinical practice in long-term responders across Europe; (ii) differences in radiological assessment schedules that might have led to the benefit of a particular sequence being slightly overestimated; (iii) a relatively short follow-up period in 14 TKI–mTORi patients at the time of data analysis although short follow-up did not influence reliability of estimates in a sensitivity analysis; (iv) lack of information on cytokine pretreatment and dose reductions; (v) inability to relate OS to sequence because of subsequent therapies; (vi) an emphasis on second-line sorafenib rather than axitinib which had not yet been approved when the patients were being treated.

conclusion

Given the limited number of drug classes available to treat patients with m-ccRCC, physicians inevitably face the decision whether to reintroduce a drug belonging to an earlier therapeutic class that yielded a clinically significant response or to switch to another class of drug. Our findings suggest that a second-line TKI might be a pragmatic and beneficial option in long-term responders to a first-line TKI (between 11 and 22 months) in whom drug toxicity is manageable. This would now require confirmation in a prospective trial.

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disclosure

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